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FIG. 1

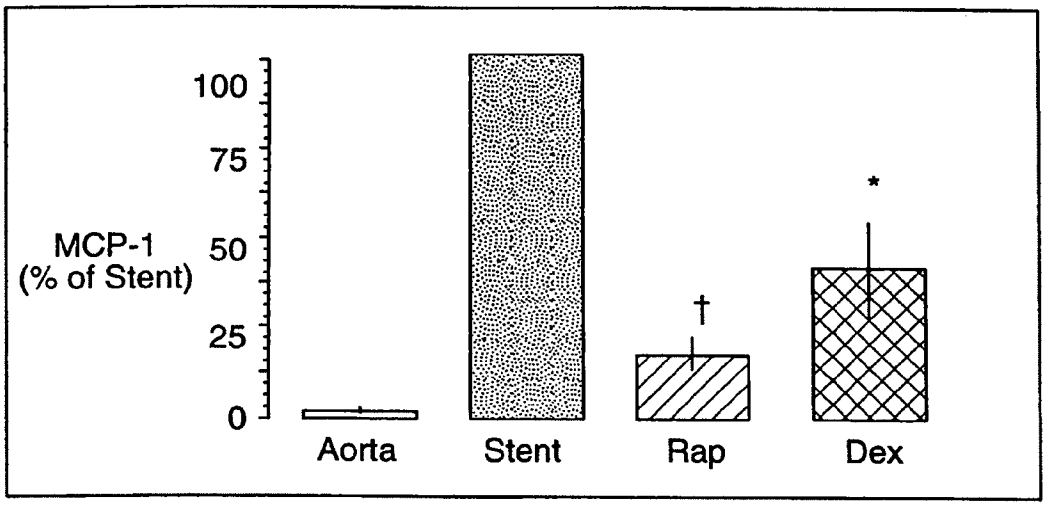


FIG. 2

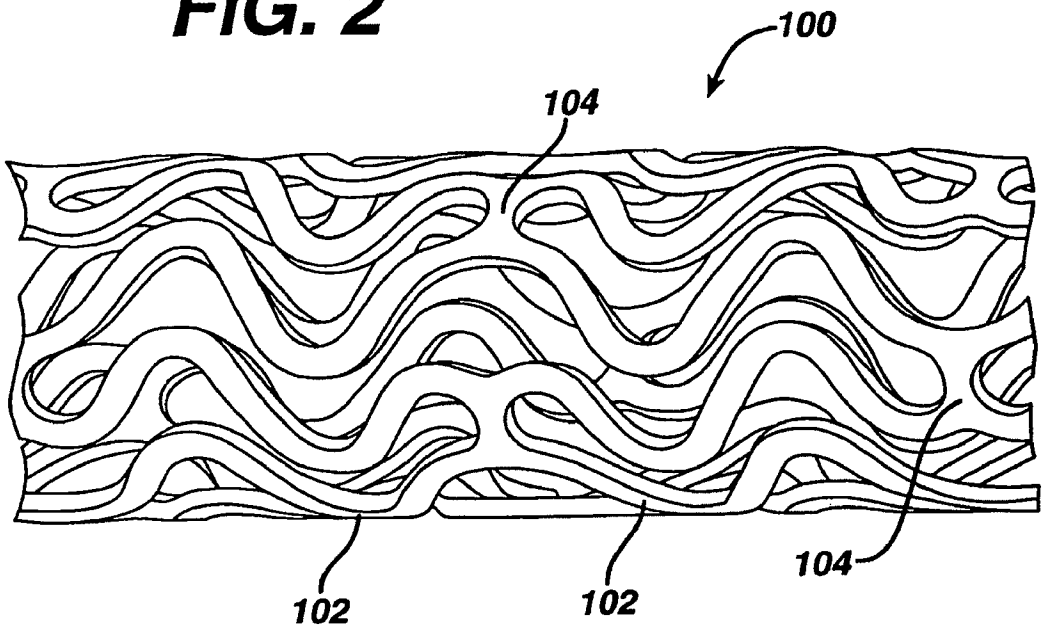
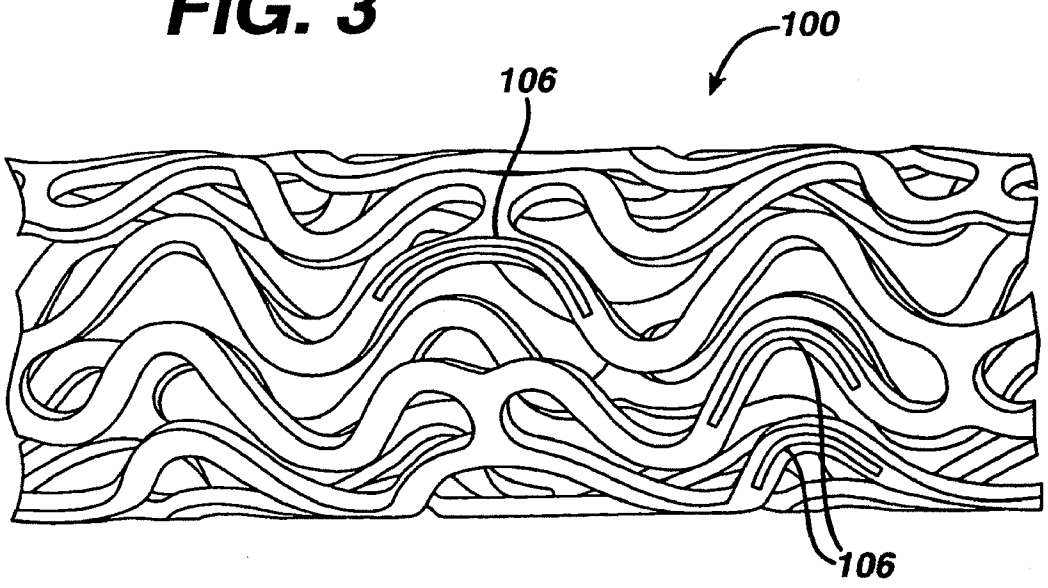


FIG. 3



DRUG/DRUG DELIVERY SYSTEMS FOR THE PREVENTION AND TREATMENT OF VASCULAR DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 09/850,293, filed May 7, 2001, now abandoned, which in turn claims priority of U.S. Provisional Application No. 60/263,979, filed Jan. 25, 2001, U.S. Provisional Application No. 60/263,806, filed January 24, 2001, U.S. Provisional Application No. 60/262,614, filed Jan. 18, 2001, U.S. Provisional Application No. 60/262,461, filed Jan. 18, 2001, and is a continuation-in-part of U.S. Application No. 09,575,480, filed May 19, 2000, now pending, which in turn claims priority of U.S. Provisional Application No. 60/204,4 17, filed May 12, 2000.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to drugs and drug delivery systems for the prevention and treatment of vascular disease, and more particularly to drugs and drug delivery systems for the prevention and treatment of neointimal hyperplasia.

2. Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs with nutrients. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery. Percutaneous transluminal coronary angioplasty is the predominant treatment for coronary vessel stenosis. The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure and restenosis which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the

smooth muscle cells and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985).

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, fibroblast growth factor, epidermal growth factor, thrombin, etc., released from platelets, invading macrophages and/or leukocytes, or directly from the smooth muscle cells provoke proliferative and migratory responses in medial smooth muscle cells. These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within one to two days post-injury and peaks several days thereafter (Campbell and Campbell, 1987; Clowes and Schwartz, 1985).

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima, usually within seven to fourteen days post-injury. The newly formed tissue is called neointima. The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling.

Simultaneous with local proliferation and migration, inflammatory cells invade the site of vascular injury. Within three to seven days post-injury, inflammatory cells have migrated to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al., 1993; Edelman et al., 1998). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A. W. and Karnovsky M., Nature 265: 25-26, 1977; Guyton, J. R. et al., Circ. Res., 46: 625-634, 1980; Clowes, A. W. and Clowes, M. M., Lab. Invest. 52: 611-616, 1985; Clowes, A. W. and Clowes, M. M., Circ. Res. 58: 839-845, 1986; Majesky et al., Circ. Res. 61: 296-300, 1987; Snow et al., Am. J. Pathol. 137: 313-330, 1990; Okada, T. et al., Neurosurgery 25: 92-98, 1989), colchicine (Currier, J. W. et al., Circ. 80: 11-66, 1989), taxol (Sollot, S. J. et al., J. Clin. Invest. 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., Science, 245: 186-188, 1989), angiopeptin (Lundergan, C. F. et al. Am. J. Cardiol. 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., Science 253: 1129-1132, 1991), terbinafine (Nemecek, G. M. et al., J. Pharmacol. Exp. Thera. 248: 1167-1174, 1989), trapidil (Liu, M. W. et al., Circ. 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327-332, 1996), interferon-gamma (Hansson, G. K. and Holm, J., Circ. 84: 1266-1272, 1991), rapamycin (Marx, S. O. et al., Circ. Res. 76: 412-417, 1995), corticosteroids (Colburn, M. D. et al., J. Vasc. Surg. 15:

510-518, 1992), see also Berk, B. C. et al., J. Am. Coll. Cardiol. 17: 111B-117B, 1991), ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767-775, 1996), fusion toxins (Farb, A. et al., Circ. Res. 80: 542-550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M. W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Anti-proliferative effects on smooth muscle cells in vitro have been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991). The platelet GP IIb/IIIa receptor, antagonist, Reopro is still under study but has not shown promising results for the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993: Serruys, P. W. et al., 1993). Recent observations suggest that the antilipid/antioxidant agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al., 1997; Yokoi, et al., 1997). Probucol is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty. Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., 1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven effective in significantly reducing restenosis. Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

Accordingly, there exists a need for effective drugs and drug delivery systems for the effective prevention and treatment of neointimal thickening that occurs after percutaneous transluminal coronary angioplasty and stent implantation.

SUMMARY OF THE INVENTION

The drugs and drug delivery systems of the present invention provide a means for overcoming the difficulties associated with the methods and devices currently in use as briefly described above.

In accordance with one aspect, the present invention is directed to a method for the prevention of constrictive remodeling. The method comprises the controlled delivery, by release from an intraluminal medical device, of a compound in therapeutic dosage amounts.

In accordance with another aspect, the present invention is directed to a drug delivery device. The drug delivery device comprises an intraluminal medical device and a therapeutic dosage of an agent releasably affixed to the intraluminal medical device for the treatment of constrictive vascular remodeling.

The drugs and drug delivery systems of the present invention utilize a stent or graft in combination with rapamycin or other drugs/agents/compounds to prevent and treat neointimal hyperplasia, i.e. restenosis, following percutaneous transluminal coronary angioplasty and stent implantation. It has been determined that rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. It has also been determined that rapamycin eluting stent coatings produce superior effects in humans, when compared to animals, with respect to the magnitude and duration of the reduction in neointimal hyperplasia. Rapamycin administration from a local delivery platform also produces an anti-inflammatory effect in the vessel wall that is distinct from and complimentary to its smooth muscle cell anti-proliferative effect. In addition, it has also been demonstrated that rapamycin inhibits constrictive vascular remodeling in humans.

Other drugs, agents or compounds which mimic certain actions of rapamycin may also be utilized in combination with local delivery systems or platforms.

The local administration of drugs, agents or compounds to stented vessels have the additional therapeutic benefit of higher tissue concentration than that which would be achievable through the systemic administration of the same drugs, agents or compounds. Other benefits include reduced systemic toxicity, single treatment, and ease of administration. An additional benefit of a local delivery device and drug, agent or compound therapy may be to reduce the dose of the therapeutic drugs, agents or compounds and thus limit their toxicity, while still achieving a reduction in restenosis.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

FIG. **1** is a chart indicating the effectiveness of rapamycin as an anti-inflammatory relative to other anti-inflammatories.

FIG. **2** is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern.

FIG. **3** is a perspective view of the stent of FIG. **1** having reservoirs in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As stated above, the proliferation of vascular smooth muscle cells in response to mitogenic stimuli that are released during balloon angioplasty and stent implantation is the primary cause of neointimal hyperplasia. Excessive neointimal hyperplasia can often lead to impairment of blood flow, cardiac ischemia and the need for a repeat intervention in selected patients in high risk treatment groups. Yet repeat revascularization incurs risk of patient morbidity and mortality while adding significantly to the cost of health care. Given the widespread use of stents in interventional practice, there is a clear need for safe and effective inhibitors of neointimal hyperplasia.

Rapamycin is a macroyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U.S. Pat. No. 3,929,992. It has been found that rapamycin inhibits the proliferation of vascular smooth muscle cells in vivo. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls.

Rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. In addition, rapamycin reduces the other effects caused by vascular injury, for example, inflammation. The operation and various functions of rapamycin are described in detail below. Rapamycin as used throughout this application shall include rapamycin, rapamycin analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty. Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late G1 phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically. This is the basis for its immunosuppresive activity and its ability to prevent graft rejection.

The molecular events that are responsible for the actions of rapamycin, a known anti-proliferative, which acts to reduce the magnitude and duration of neointimal hyperplasia, are still being elucidated. It is known, however, that rapamycin enters cells and binds to a high-affinity cytosolic protein called FKBP12. The complex of rapamycin and

FKPB12 in turn binds to and inhibits a phosphoinositide (PI)-3 kinase called the "mammalian Target of Rapamycin" or TOR. TOR is a protein kinase that plays a key role in mediating the downstream signaling events associated with mitogenic growth factors and cytokines in smooth muscle cells and T lymphocytes. These events include phosphorylation of p27, phosphorylation of p70 s6 kinase and phosphorylation of 4BP-1, an important regulator of protein translation.

It is recognized that rapamycin reduces restenosis by inhibiting neointimal hyperplasia. However, there is evidence that rapamycin may also inhibit the other major component of restenosis, namely, negative remodeling. Remodeling is a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in lumenal area over time, generally a period of approximately three to six months in humans.

Negative or constrictive vascular remodeling may be quantified angiographically as the percent diameter stenosis at the lesion site where there is no stent to obstruct the process. If late lumen loss is abolished in-lesion, it may be inferred that negative remodeling has been inhibited. Another method of determining the degree of remodeling involves measuring in-lesion external elastic lamina area using intravascular ultrasound (IVUS). Intravascular ultrasound is a technique that can image the external elastic lamina as well as the vascular lumen. Changes in the external elastic lamina proximal and distal to the stent from the post-procedural timepoint to four-month and twelve-month follow-ups are reflective of remodeling changes.

Evidence that rapamycin exerts an effect on remodeling comes from human implant studies with rapamycin coated stents showing a very low degree of restenosis in-lesion as well as in-stent. In-lesion parameters are usually measured approximately five millimeters on either side of the stent i.e. proximal and distal. Since the stent is not present to control remodeling in these zones which are still affected by balloon expansion, it may be inferred that rapamycin is preventing vascular remodeling.

The data in Table 1 below illustrate that in-lesion percent diameter stenosis remains low in the rapamycin treated groups, even at twelve months. Accordingly, these results support the hypothesis that rapamycin reduces remodeling.

TABLE 1.0

Angiographic In-Lesion Percent Diameter Stenosis (%, mean ± SD and "n=") In Patients Who Received a Rapamycin-Coated Stent

Coating Group	Post Placement	4–6 month Follow Up	12 month Follow Up
Brazil	10.6 ± 5.7 (30)	13.6 ± 8.6 (30)	22.3 ± 7.2 (15)
Netherlands	14.7 ± 8.8	22.4 ± 6.4	—

Additional evidence supporting a reduction in negative remodeling with rapamycin comes from intravascular ultrasound data that was obtained from a first-in-man clinical program as illustrated in Table 2 below.

TABLE 2.0

Matched IVUS data in Patients Who Received a Rapamycin-Coated Stent

IVUS Parameter	Post (n=)	4-Month Follow-Up (n=)	12-Month Follow-Up (n=)
Mean proximal vessel area (mm^2)	16.53 ± 3.53 (27)	16.31 ± 4.36 (28)	13.96 ± 2.26 (13)
Mean distal vessel area (mm^2)	13.12 ± 3.68 (26)	13.53 ± 4.17 (26)	12.49 ± 3.25 (14)

The data illustrated that there is minimal loss of vessel area proximally or distally which indicates that inhibition of negative remodeling has occurred in vessels treated with rapamycin-coated stents.

Other than the stent itself, there have been no effective solutions to the problem of vascular remodeling. Accordingly, rapamycin may represent a biological approach to controlling the vascular remodeling phenomenon.

It may be hypothesized that rapamycin acts to reduce negative remodeling in several ways. By specifically blocking the proliferation of fibroblasts in the vascular wall in response to injury, rapamycin may reduce the formation of vascular scar tissue. Rapamycin may also affect the translation of key proteins involved in collagen formation or metabolism.

Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

In a preferred embodiment, the rapamycin is delivered by a local delivery device to control negative remodeling of an arterial segment after balloon angioplasty as a means of reducing or preventing restenosis. While any delivery device may be utilized, it is preferred that the delivery device comprises a stent that includes a coating or sheath which elutes or releases rapamycin. The delivery system for such a device may comprise a local infusion catheter that delivers rapamycin at a rate controlled by the administrator.

Rapamycin may also be delivered systemically using an oral dosage form or a chronic injectible depot form or a patch to deliver rapamycin for a period ranging from about seven to forty-five days to achieve vascular tissue levels that are sufficient to inhibit negative remodeling. Such treatment is to be used to reduce or prevent restenosis when administered several days prior to elective angioplasty with or without a stent.

Data generated in porcine and rabbit models show that the release of rapamycin into the vascular wall from a nonerodible polymeric stent coating in a range of doses (35-430 ug/5-18 mm coronary stent) produces a peak fifty to fifty-five percent reduction in neointimal hyperplasia as set forth in Table 3 below. This reduction, which is maximal at about twenty-eight to thirty days, is typically not sustained in the range of ninety to one hundred eighty days in the porcine model as set forth in Table 4 below.

TABLE 3.0

Animal Studies with Rapamycin-coated stents. Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal
Porcine							
98009	14 days	Metal		8	2.04 ± 0.17		
		1X + rapamycin	153 μg	8	1.66 ± 0.17*	-42%	-19%
		1X + TC300 + rapamycin	155 μg	8	1.51 ± 0.19*	-47%	-26%
99005	28 days	Metal		10	2.29 ± 0.21		
				9	3.91 ± 0.60**		
		1X + TC30 + rapamycin	130 μg	8	2.81 ± 0.34		+23%
		1X + TC100 + rapamycin	120 μg	9	2.62 ± 0.21		+14%
99006	28 days	Metal		12	4.57 ± 0.46		
		EVA/BMA 3X		12	5.02 ± 0.62		+10%
		1X + rapamycin	125 μg	11	2.84 ± 0.31* **	-43%	-38%
		3X + rapamycin	430 μg	12	3.06 ± 0.17* **	-39%	-33%
		3X + rapamycin	157 μg	12	2.77 ± 0.41* **	-45%	-39%
99011	28 days	Metal		11	3.09 ± 0.27		
				11	4.52 ± 0.37		
		1X + rapamycin	189 μg	14	3.05 ± 0.35		-1%
		3X + rapamycin/dex	182/363 μg	14	2.72 ± 0.71		-12%
99021	60 days	Metal		12	2.14 ± 0.25		
		1X + rapamycin	181 μg	12	2.95 ± 0.38		+38%
99034	28 days	Metal		8	5.24 ± 0.58		
		1X + rapamycin	186 μg	8	2.47 ± 0.33**		-53%
		3X + rapamycin/dex	185/369 μg	6	2.42 ± 0.64**		-54%
20001	28 days	Metal		6	1.81 ± 0.09		
		1X + rapamycin	172 μg	5	1.66 ± 0.44		-8%
20007							
	30 days	Metal		9	2.94 ± 0.43		
		1XTC + rapamycin	155 μg	10	1.40 ± 0.11*		-52%*
Rabbit							
99019	28 days	Metal		8	1.20 ± 0.07		

TABLE 3.0-continued

Animal Studies with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal
		EVA/BMA 1X		10	1.26 ± 0.16		+5%
		1X + rapamycin	64 μg	9	0.92 ± 0.14	−27%	−23%
		1X + rapamycin	196 μg	10	0.66 ± 0.12* **	−48%	−45%
99020	28 days	Metal		12	1.18 ± 0.10		
		EVA/BMA 1X + rapamycin	197 μg	8	0.81 ± 0.16		−32%

[1]Stent nomenclature: EVA/BMA 1X, 2X, and 3X signifies approx. 500 μg, 1000 μg, and 1500 μg total mass (polymer + drug), respectively. TC, top coat of 30 μg, 100 μg, or 300 μg drug-free BMA; Biphasic; 2 × 1X layers of rapamycin in EVA/BMA spearated by a 100 μg drug-free BMA layer.
[2]0.25 mg/kg/d × 14 d preceeded by a loading dose of 0.5 mg/kg/d × 3 d prior to stent implantation.
*p < 0.05 from EVA/BMA control.
**p < 0.05 from Metal;
#Inflammation score: (0 = essentially no intimal involvement; 1 = <25% intima involved; 2 =≧25% intima involved; 3 = >50% intima involved).

TABLE 4.0

180 day Porcine Study with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal	Inflammation Score #
20007	3 days	Metal		10	0.38 ± 0.06			1.05 ± 0.06
(ETP-2-002233-P)		1XTC + rapamycin	155 μg	10	0.29 ± 0.03		−24%	1.08 ± 0.04
	30 days	Metal		9	2.94 ± 0.43			0.11 ± 0.08
		1XTC + rapamycin	155 μg	10	1.40 ± 0.11*		−52%*	0.25 ± 0.10
	90 days	Metal		10	3.45 ± 0.34			0.20 ± 0.08
		1XTC + rapamycin	155 μg	10	3.03 ± 0.29		−12%	0.80 ± 0.23
		1X + rapamycin	171 μg	10	2.86 ± 0.35		−17%	0.60 ± 0.23
	180 days	Metal		10	3.65 ± 0.39			0.65 ± 0.21
		1XTC + rapamycin	155 μg	10	3.34 ± 0.31		−8%	1.50 ± 0.34
		1X + rapamycin	171 μg	10	3.87 ± 0.28		+6%	1.68 ± 0.37

The release of rapamycin into the vascular wall of a human from a nonerodible polymeric stent coating provides superior results with respect to the magnitude and duration of the reduction in neointimal hyperplasia within the stent as compared to the vascular walls of animals as set forth above.

Humans implanted with a rapamycin coated stent comprising rapamycin in the same dose range as studied in animal models using the same polymeric matrix, as described above, reveal a much more profound reduction in neointimal hyperplasia than observed in animal models, based on the magnitude and duration of reduction in neointima. The human clinical response to rapamycin reveals essentially total abolition of neointimal hyperplasia inside the stent using both angiographic and intravascular ultrasound measurements. These results are sustained for at least one year as set forth in Table 5 below.

TABLE 5.0

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
Procedure Success (QCA)	100.0% (45/45)	[92.1%, 100.0%]
4-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	4.8% ± 6.1% (30)	[2.6%, 7.0%]
Range (min, max)	(−8.2%, 14.9%)	
6-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 7.6% (13)	[4.8%, 13.0%]
Range (min, max)	(−2.9%, 20.4%)	
12-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 6.1% (15)	[5.8%, 12.0%]
Range (min, max)	(−3.0%, 22.0%)	

TABLE 5.0-continued

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent		
Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
4-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.00 ± 0.29 (30)	[−0.10, 0.10]
Range (min, max)	(−0.51, 0.45)	
6-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.25 ± 0.27 (13)	[0.10, 0.39]
Range (min, max)	(−0.51, 0.91)	
12-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.11 ± 0.36 (15)	[−0.08, 0.29]
Range (min, max)	(−0.51, 0.82)	
4-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	10.48% ± 2.78% (28)	[9.45%, 11.51%]
Range (min, max)	(4.60%, 16.35%)	
6-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	7.22% ± 4.60% (13)	[4.72%, 9.72%],
Range (min, max)	(3.82%, 19.88%)	
12-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	2.11% ± 5.28% (15)	[0.00%, 4.78%],
Range (min, max)	(0.00%, 19.89%)	
6-month Target Lesion Revascularization (TLR)	0.0% (0/30)	[0.0%, 9.5%]
12-month Target Lesion Revascularization (TLR)	0.0% (0/15)	[0.0%, 18.1%]

QCA = Quantitative Coronary Angiography
SD = Standard Deviation
IVUS = Intravascular Ultrasound

Rapamycin produces an unexpected benefit in humans when delivered from a stent by causing a profound reduction in in-stent neointimal hyperplasia that is sustained for at least one year. The magnitude and duration of this benefit in humans is not predicted from animal model data. Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

These results may be due to a number of factors. For example, the greater effectiveness of rapamycin in humans is due to greater sensitivity of its mechanism(s) of action toward the pathophysiology of human vascular lesions compared to the pathophysiology of animal models of angioplasty. In addition, the combination of the dose applied to the stent and the polymer coating that controls the release of the drug is important in the effectiveness of the drug.

As stated above, rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty injury. Also, it is known that rapamycin prevents T-cell proliferation and differentiation when administered systemically. It has also been determined that rapamycin exerts a local inflammatory effect in the vessel wall when administered from a stent in low doses for a sustained period of time (approximately two to six weeks). The local anti-inflammatory benefit is profound and unexpected. In combination with the smooth muscle anti-proliferative effect, this dual mode of action of rapamycin may be responsible for its exceptional efficacy.

Accordingly, rapamycin delivered from a local device platform, reduces neointimal hyperplasia by a combination of anti-inflammatory and smooth muscle anti-proliferative effects. Rapamycin used in this context means rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin. Local device platforms include stent coatings, stent sheaths, grafts and local drug infusion catheters or porous balloons or any other suitable means for the in situ or local delivery of drugs, agents or compounds.

The anti-inflammatory effect of rapamycin is evident in data from an experiment, illustrated in Table 6, in which rapamycin delivered from a stent was compared with dexamethasone delivered from a stent. Dexamethasone, a potent steroidal anti-inflammatory agent, was used as a reference standard. Although dexamethasone is able to reduce inflammation scores, rapamycin is far more effective than dexamethasone in reducing inflammation scores. In addition, rapamycin significantly reduces neointimal hyperplasia, unlike dexamethasone.

TABLE 6.0

Group Rapamycin Rap	N=	Neointimal Area (mm^2)	% Area Stenosis	Inflammation Score
Uncoated	8	5.24 ± 1.65	54 ± 19	0.97 ± 1.00
Dexamethasone (Dex)	8	4.31 ± 3.02	45 ± 31	0.39 ± 0.24
Rapamycin (Rap)	7	2.47 ± 0.94*	26 ± 10*	0.13 ± 0.19*
Rap + Dex	6	2.42 ± 1.58*	26 ± 18*	0.17 ± 0.30*

*= significance level $P < 0.05$

Rapamycin has also been found to reduce cytokine levels in vascular tissue when delivered from a stent. The data in FIG. 1 illustrates that rapamycin is highly effective in reducing monocyte chemotactic protein (MCP-1) levels in

the vascular wall. MCP-1 is an example of a proinflammatory/chemotactic cytokine that is elaborated during vessel injury. Reduction in MCP-1 illustrates the beneficial effect of rapamycin in reducing the expression of proinflammatory mediators and contributing to the anti-inflammatory effect of rapamycin delivered locally from a stent. It is recognized that vascular inflammation in response to injury is a major contributor to the development of neointimal hyperplasia.

Since rapamycin may be shown to inhibit local inflammatory events in the vessel it is believed that this could explain the unexpected superiority of rapamycin in inhibiting neointima.

As set forth above, rapamycin functions on a number of levels to produce such desired effects as the prevention of T-cell proliferation, the inhibition of negative remodeling, the reduction of inflammation, and the prevention of smooth muscle cell proliferation. While the exact mechanisms of these functions are not completely known, the mechanisms that have been identified may be expanded upon.

Studies with rapamycin suggest that the prevention of smooth muscle cell proliferation by blockade of the cell cycle is a valid strategy for reducing neointimal hyperplasia. Dramatic and sustained reductions in late lumen loss and neointimal plaque volume have been observed in patients receiving rapamycin delivered locally from a stent. The present invention expands upon the mechanism of rapamycin to include additional approaches to inhibit the cell cycle and reduce neointimal hyperplasia without producing toxicity.

The cell cycle is a tightly controlled biochemical cascade of events that regulate the process of cell replication. When cells are stimulated by appropriate growth factors, they move from G_0 (quiescence) to the G1 phase of the cell cycle. Selective inhibition of the cell cycle in the G1 phase, prior to DNA replication (S phase), may offer therapeutic advantages of cell preservation and viability while retaining anti-proliferative efficacy when compared to therapeutics that act later in the cell cycle i.e. at S, G2 or M phase.

Accordingly, the prevention of intimal hyperplasia in blood vessels and other conduit vessels in the body may be achieved using cell cycle inhibitors that act selectively at the G1 phase of the cell cycle. These inhibitors of the G1 phase of the cell cycle may be small molecules, peptides, proteins, oligonucleotides or DNA sequences. More specifically, these drugs or agents include inhibitors of cyclin dependent kinases (cdk's) involved with the progression of the cell cycle through the G1 phase, in particular cdk2 and cdk4.

Examples of drugs, agents or compounds that act selectively at the G1 phase of the cell cycle include small molecules such as flavopiridol and its structural analogs that have been found to inhibit cell cycle in the late G1 phase by antagonism of cyclin dependent kinases. Therapeutic agents that elevate an endogenous kinase inhibitory protein^{kip} called P27, sometimes referred to as P27^{kip1}, that selectively inhibits cyclin dependent kinases may be utilized. This includes small molecules, peptides and proteins that either block the degradation of P27 or enhance the cellular production of P27, including gene vectors that can transfact the gene to produce P27. Staurosporin and related small molecules that block the cell cycle by inhibiting protein kinases may be utilized. Protein kinase inhibitors, including the class of tyrphostins that selectively inhibit protein kinases to antagonize signal transduction in smooth muscle in response to a broad range of growth factors such as PDGF and FGF may also be utilized.

Any of the drugs, agents or compounds discussed above may be administered either systemically, for example, orally, intravenously, intramuscularly, subcutaneously, nasally or intradermally, or locally, for example, stent coating, stent covering or local delivery catheter. In addition, the drugs or agents discussed above may be formulated for fast-release or slow release with the objective of maintaining the drugs or agents in contact with target tissues for a period ranging from three days to eight weeks.

As set forth above, the complex of rapamycin and FKPB12 binds to and inhibits a phosphoinositide (PI)-3 kinase called the mammalian Target of Rapamycin or TOR. An antagonist of the catalytic activity of TOR, functioning as either an active site inhibitor or as an allosteric modulator, i.e. an indirect inhibitor that allosterically modulates, would mimic the actions of rapamycin but bypass the requirement for FKBP12. The potential advantages of a direct inhibitor of TOR include better tissue penetration and better physical/chemical stability. In addition, other potential advantages include greater selectivity and specificity of action due to the specificity of an antagonist for one of multiple isoforms of TOR that may exist in different tissues, and a potentially different spectrum of downstream effects leading to greater drug efficacy and/or safety.

The inhibitor may be a small organic molecule (approximate mw<1000), which is either a synthetic or naturally derived product. Wortmanin may be an agent which inhibits the function of this class of proteins. It may also be a peptide or an oligonucleotide sequence. The inhibitor may be administered either sytemically (orally, intravenously, intramuscularly, subcutaneously, nasally, or intradermally) or locally (stent coating, stent covering, local drug delivery catheter). For example, the inhibitor may be released into the vascular wall of a human from a nonerodible polymeric stent coating. In addition, the inhibitor may be formulated for fast-release or slow release with the objective of maintaining the rapamycin or other drug, agent or compound in contact with target tissues for a period ranging from three days to eight weeks.

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, the use of drugs, agents or compounds which prevent inflammation and proliferation, or prevent proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

The local delivery of drugs, agents or compounds from a stent has the following advantages; namely, the prevention of vessel recoil and remodeling through the scaffolding action of the stent and the drugs, agents or compounds and the prevention of multiple components of neointimal hyperplasia. This local administration of drugs, agents or compounds to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations would be achievable than that which would occur with systemic administration, reduced systemic toxicity, and single treatment and ease of administration. An additional benefit of drug therapy may be to reduce the dose of the therapeutic compounds, thereby limiting their toxicity, while still achieving a reduction in restenosis.

There are a multiplicity of different stents that may be utilized following percutaneous transluminal coronary angioplasty. Although any number of stents may be utilized in accordance with the present invention, for simplicity, one particular stent will be described in exemplary embodiments of the present invention. The skilled artisan will recognize that any number of stents may be utilized in connection with the present invention.

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device in situ. A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen. As set forth below, self-expanding stents may also be utilized.

FIG. **2** illustrates an exemplary stent **100** which may be utilized in accordance with an exemplary embodiment of the present invention. The expandable cylindrical stent **100** comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open, more particularly for protecting a segment of artery from restenosis after angioplasty. The stent **100** may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent **100** is axially flexible and when flexed at a band, the stent **100** avoids any externally-protruding component parts.

The stent **100** generally comprises first and second ends with an intermediate section therebetween. The stent **100** has a longitudinal axis and comprises a plurality of longitudinally disposed bands **102**, wherein each band **102** defines a generally continuous wave along a line segment parallel to the longitudinal axis. A plurality of circumferentially arranged links **104** maintain the bands **102** in a substantially tubular structure. Essentially, each longitudinally disposed band **102** is connected at a plurality of periodic locations, by a short circumferentially arranged link **104** to an adjacent band **102**. The wave associated with each of the bands **102** has approximately the same fundamental spatial frequency in the intermediate section, and the bands **102** are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another. As illustrated in the figure, each longitudinally arranged band **102** undulates through approximately two cycles before there is a link to an adjacent band.

The stent **100** may be fabricated utilizing any number of methods. For example, the stent **100** may be fabricated from a hollow or formed stainless steel tube that may be machined using lasers, electric discharge milling, chemical etching or other means. The stent **100** is inserted into the body and placed at the desired site in an unexpanded form. In one embodiment, expansion may be effected in a blood vessel by a balloon catheter, where the final diameter of the stent **100** is a function of the diameter of the balloon catheter used.

It should be appreciated that a stent **100** in accordance with the present invention may be embodied in a shape-memory material, including, for example, an appropriate alloy of nickel and titanium. In this embodiment, after the stent **100** has been formed it may be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means, wherein the insertion means include a suitable catheter, or flexible rod. On emerging from the catheter, the stent **100** may be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure, temperature or electrical stimulation.

FIG. **3** illustrates an exemplary embodiment of the present invention utilizing the stent **100** illustrated in FIG. **2**. As illustrated, the stent **100** may be modified to comprise a reservoir **106**. Each of the reservoirs may be opened or closed as desired. These reservoirs **106** may be specifically designed to hold the drug, agent, compound or combinations thereof to be delivered. Regardless of the design of the stent **100**, it is preferable to have the drug, agent, compound or combinations thereof dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the bands **102** is preferably sized to adequately apply the drug/drug combination dosage at the desired location and in the desired amount.

In an alternate exemplary embodiment, the entire inner and outer surface of the stent **100** may be coated with various drug and drug combinations in therapeutic dosage amounts. A detailed description of exemplary coating techniques is described below.

Rapamycin or any of the drugs, agents or compounds described above may be incorporated into or affixed to the stent in a number of ways and utilizing any number of biocompatible materials. In the exemplary embodiment, the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue. The rapamycin preferably remains on the stent for at least three days up to approximately six months and more preferably between seven and thirty days.

Any number of non-erodible polymers may be utilized in conjunction with rapamycin. In the exemplary embodiment, the polymeric matrix comprises two layers. The base layer comprises a solution of ethylene-co-vinylacetate and polybutylmethacrylate. The rapamycin is incorporated into this layer. The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the rapamycin from eluting too quickly and entering the surrounding tissues. The thickness of the outer layer or top coat determines the rate at which the rapamycin elutes from the matrix. Essentially, the rapamycin elutes from the matrix by diffusion through the polymer molecules. Polymers tend to move, thereby allowing solids, liquids and gases to escape therefrom. The total thickness of the polymeric matrix is in the range from about 1 micron to about 20 microns or greater. In a preferred exemplary embodiment, the base layer, including the polymer and drug, has a thickness in the range from about 8 microns to about 12 microns and the outer layer has a thickness in the range from about 1 micron to about 2 microns.

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways. For example, the solution may be sprayed onto the stent or the stent may be dipped into the solution. In a preferred embodiment, the solution is sprayed onto the stent and then allowed to dry. In another exemplary embodiment, the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste may be reduced and more control over the thickness of the coat may be achieved.

Since rapamycin works by entering the surrounding tissue, it is preferably only affixed to the surface of the stent making contact with one tissue. Typically, only the outer surface of the stent makes contact with the tissue. Accord-

ingly, in a preferred embodiment, only the outer surface of the stent is coated with rapamycin. For other drugs, agents or compounds, the entire stent may be coated.

It is important to note that different polymers may be utilized for different stents. For example, in the above-described embodiment, ethylene-co-vinylacetate and polybutylmethacrylate are utilized to form the polymeric matrix. This matrix works well with stainless steel stents. Other polymers may be utilized more effectively with stents formed from other materials, including materials that exhibit superelastic properties such as alloys of nickel and titanium.

Although shown and described is what is believed to be the most practical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

What is claimed is:

1. A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography.

2. A drug delivery device according to claim **1** that provides an in- stent late loss in diameter at 12 months following implantation in a human of less than about 0.3 mm, as measured by quantitative coronary angiography.

3. A drug delivery device according to claim **1** or **2** that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22%, as measured by quantitative coronary angiography.

4. A drug delivery device according to claim **3** that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 15%, as measured by quantitative coronary angiography.

5. A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

6. A drug delivery device according to claim **5** that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

7. A drug delivery device according to claim **5** or **6** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

8. A drug delivery device according to claim **7** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

9. A method of inhibiting neointimal proliferation in a human coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

10. A method according to claim **9** that provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

11. A method according to claim **9** or **10** that provides an in-stent diameter stenosis at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

12. A method according to claim **11** that provides an in-stent diameter stenosis at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

13. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

14. A method according to claim **13** that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

15. A method according to claim **13** or **14** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

16. A method according to claim **15** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

17. The drug delivery device according to any one of claims **1**, **2**, **4** or **5** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

18. The drug delivery device according to to any one of claims **1**, **2**, **4** or **5** that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

19. The drug delivery device according to any one of claims **1**, **2**, **4** or **5** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.

20. The drug delivery device according to claim **19** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

21. The drug delivery device according to claim **19** that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

22. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

23. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.

24. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

25. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said drug delivery device releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

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JACC

Journal of the American College of Cardiology/*Contents in brief*

OCTOBER 1995 VOLUME 26 NUMBER 4

CLINICAL STUDIES

ELECTROPHYSIOLOGY

MYOCARDIAL ISCHEMIA

MYOCARDIAL INFARCTION

INTERVENTIONAL CARDIOLOGY

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The Subcutaneous Heparin and Angioplasty Restenosis Prevention (SHARP) Trial

Results of a Multicenter Randomized Trial Investigating the Effects of High Dose Unfractionated Heparin on Angiographic Restenosis and Clinical Outcome

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Objectives. We sought to determine whether 12,500 IU of unfractionated heparin given subcutaneously twice daily for 4 months after percutaneous transluminal coronary angioplasty beneficially influences the subsequent rate of angiographic restenosis and the incidence of clinical events.

Background. Heparin has been shown to exhibit powerful antiproliferative effects against smooth muscle cells in several animal models.

Methods. A randomized trial with blinded data analysis was undertaken to assess the effect of unfractionated subcutaneous heparin on angiographic restenosis after coronary angioplasty. After successful angioplasty, patients were randomized to receive no heparin or 12,500 IU of heparin given subcutaneously twice daily for 4 months. Quantitative coronary angiography was performed before angioplasty, immediately after angioplasty and at follow-up ("early" [before 4 months] or electively [at 4 months]).

Results. The study group comprised 339 patients, 167 randomly assigned to receive heparin, 172 to receive no heparin. Repeat cardiac catheterization was performed in 90% of randomized patients. At early and elective restudy (mean 4.2 months), the mean ± SD difference in minimal lumen diameter between the postangioplasty and follow-up measurement was −0.55 ± 0.58 mm for the no heparin group and −0.43 ± 0.59 mm for the heparin group (p = NS). Clinical events during the follow-up period did not differ significantly between groups: fatal myocardial infarction (1 patient in each group), coronary bypass grafting (5 patients in each group), repeat angioplasty (12 in the no heparin, 6 in the heparin group), angina at 4-month assessment (33% in the no heparin, 32% in the heparin group).

Conclusions. Long-term treatment with high dose subcutaneous heparin (12,500 IU twice daily) for 4 months did not favorably influence angiographic or clinical outcome after coronary angioplasty.

(J Am Coll Cardiol 1995;26:947–54)

Percutaneous transluminal coronary angioplasty is a widely accepted form of treatment for symptomatic coronary artery disease. The late restenosis rate of 30% to 60% (1–5) continues to limit the longer term benefit of the procedure.

The restenotic process is characterized by elastic recoil (up to 40%) and myointimal hyperplasia (6,7), which is initiated by migration of medial smooth muscle cells from the media to the intima (8), with proliferation there after phenotypic modulation of the migrating cells. Subsequent extracellular matrix makes up the bulk of the later (>1 month) restenotic lesion. Experimental work in animal models (9–15) and from in vitro studies (16) suggests that heparin may inhibit changes in intimal smooth muscle cells and therefore influence the restenotic process.

In a large North American (enoxaparin) trial (17), low molecular weight heparin was shown to have no effect on angiographic restenosis or clinical events. The present study, referred to as the Subcutaneous Heparin and Angioplasty Restenosis Prevention (SHARP) trial, was performed to assess the value of unfractionated calcium heparin in preventing restenosis after coronary angioplasty.

Methods

Study patients. All symptomatic patients who had undergone successful coronary angioplasty (defined as visually assessed diameter stenosis <50% after angioplasty) for an angiographically proved narrowing in one or more coronary

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arteries were considered for entry into the trial in three participating regional centers (Leicester, Liverpool and Papworth, England, United Kingdom). Patients with restenotic lesions, chronic occlusions or conduit lesions were not included. Ethical approval for the trial was granted by the appropriate committees at each participating center.

Angioplasty procedure and follow-up angiography. All angioplasty procedures were performed by the femoral route with use of steerable, movable guide wire systems. Aspirin (300 mg) was given to all patients before the procedure; the use of calcium channel antagonists or beta-adrenergic blocking agents, or both, was determined by the physician in charge of the patient. After placement of the femoral artery sheath all patients received a bolus of 10,000 IU of intravenous heparin. During prolonged procedures additional heparin (5,000 IU) was given after 1 h. After the procedure and immediately on the patient's return to the ward, intravenous administration of heparin was begun at an initial dose of 1,000 IU/h. The dose of heparin was adjusted to maintain the activated partial thromboplastin time ratio to 2.0 to 3.0:1 for up to 24 h. Balloon type and size, inflation pressure and duration of inflation were selected by each operator.

Three coronary angiograms were obtained from each patient: one immediately before and one immediately after coronary angioplasty and one at follow-up (either elective [at 4 months] or "early," if clinically indicated).

Data acquisition. Quantitative analysis was performed with use of the CardioTrace system, whose results have been shown (18) to correlate well with those of the Coronary Angiography Analysis System (CAAS) using phantoms. Essentially, orthogonal views of each lesion were taken and the exact positioning of the X-ray tube and table height noted. The angiograms obtained before and after angioplasty and at follow-up were taken in the same views. Before each angiographic sequence the contrast-free catheter was filmed and at the end of the procedure the distal 20 cm was cut and saved for subsequent micrometer measurement and calibration of the analysis system. Before the postangioplasty angiogram the guide wire was removed to avoid interference with automated edge detection. Lesion characteristics were also assessed qualitatively.

All angiographic analysis was performed at the core laboratory by a single operator who had no knowledge of the patient's group. Postangioplasty angiograms were examined for dissection defined according to the modified National Heart, Lung, and Blood Institute criteria. Intracoronary thrombus was defined as the presence of a filling defect within the lumen, surrounded by contrast material seen in multiple projections in the absence of calcium within the filling defect, the persistence of contrast material within the lumen or a visible embolization of intraluminal material downstream.

The absolute values of stenosis minimal lumen diameter and reference diameter were measured by using the catheter tip as a scaling device. The reference measurement was taken from the "normal" coronary segment at the time of stenosis measurement to allow for change in the reference artery with time (19). The CardioTrace automatically adjusts for the catheter size as measured by the micrometer gauge.

Treatment allocation. After successful coronary angioplasty and on the patient's return to the ward, we sought the patient's consent to be included in this trial. Consent was sought at this time because this was a trial of successful angioplasty and subsequent restenosis. A total of 339 patients met all inclusion and exclusion criteria and gave informed written consent. A computer-generated program randomly assigned patients to receive either no heparin (no injection) or unfractionated subcutaneous heparin (12,500 IU twice daily for 4 months).

Patients randomized to the heparin group were given the injections 2 h after femoral sheath withdrawal. All patients were discharged receiving aspirin (75 to 300 mg daily) and calcium channel antagonists, nitrates and beta-adrenergic blocking agents according to operator choice.

Follow-up evaluation. Patients receiving heparin treatment had a peak plasma heparin assay performed 1 week after discharge and a weekly platelet count for the 1st 4 weeks of therapy. Anticoagulation levels were not measured, because this is the level of heparin given long-term and safely in other groups of patients.

A syringe count was performed at 2 and 4 months. If patients reported return of their angina within the 4-month follow-up period, coronary angiography was performed if the physician deemed it clinically indicated. Even if there was no evidence of restenosis patients were not required to undergo further catheterization at 4 months.

On admission for the 4-month elective catheterization, patients underwent a standard treadmill exercise test (Bruce protocol). End points for the test were the occurrence of anginal chest pain, decrease in systolic blood pressure, significant arrhythmia, or ST segment depression >1 mm 80 ms after the J point. Clinical status was assessed during the in-hospital admission for repeat catheterization.

End points. The primary end point of the SHARP trial was the within-patient change in minimal lumen diameter as determined by quantitative angiography. Postangioplasty values were obtained from the last postangioplasty angiogram after withdrawal of the guide wire. For patients admitted early who underwent repeat angioplasty, the angiogram preceding repeat balloon dilation was considered the follow-up angiogram and was recorded in exactly the same views used in the angiograms previously obtained immediately before and after angioplasty. For all other patients the planned follow-up angiogram was used.

Secondary end points were death, myocardial infarction, need for coronary artery bypass surgery and repeat coronary angioplasty. The presence and severity of angina at follow-up (early or elective) were assessed according to the Canadian Cardiovascular Society classification.

Statistical analysis. Calculations for the power of any restenosis trial are based on an arbitrary assessment of the biologic goal balanced by the side effects of the medication being tested. In an attempt to objectively determine the sort of

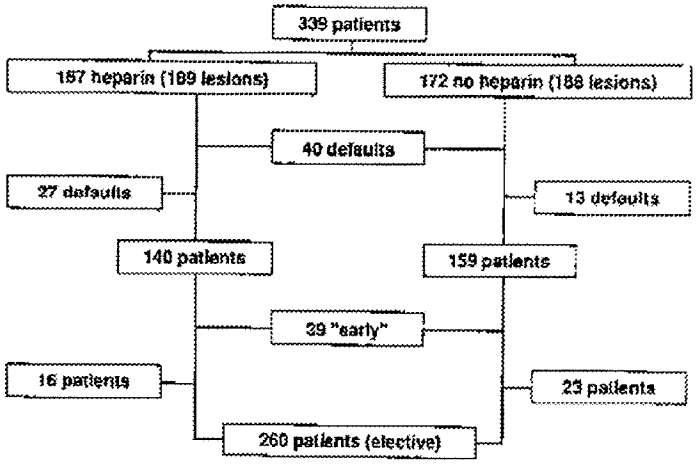


Figure 1. Patient flow from time of randomization to follow-up for the no heparin and heparin groups. "Early" and elective = cardiac catheterization performed, respectively, before 4 months and at the scheduled 4-month follow-up time.

effect we might achieve with heparin, we tested, in a pretrial study, the plasma of patients given the study dose of heparin (12,500 IU twice daily) against human smooth muscle cell growth in vitro. We found a 35% reduction in smooth muscle cell growth over 10 days (from 6.9×10^4 to 4.5×10^4) when these cells were exposed to blood from patients treated with heparin (mean level 0.3 IU/ml). Because this level of reduction is approximately equal to the arbitrarily used 33% reduction deemed important by other trialists, we used it as the aim of the treatment arm. On the basis of this 35% reduction and the results of Nobuyoshi et al. (20) and Serruys et al. (3), we estimated that the mean ± SD loss in minimal lumen diameter over a 4- to 6-month period in control patients would be −0.50 ± 0.5 mm. Assuming that diameters are normally distributed (21), we calculated that to show a reduction (the anticipated loss of lumen diameter by 35% in the heparin-treated group), 129 patients with complete angiographic follow-up were required in each group to give a power of 80% at an alpha level of 0.05. To allow for medical withdrawal of patients and patients defaulting from the trial, we aimed to recruit 340 patients. A total of 339 patients who had had successful angioplasty were recruited.

Results

Patient numbers. From February 1990 to the end of June 1993, 370 patients who had undergone successful coronary angioplasty were approached for participation in the SHARP trial. A total of 339 patients (92%) consented to participate; of these, 167 patients (189 lesions) were randomly assigned to receive subcutaneous heparin (12,500 U twice daily) and 172 patients (188 lesions) to receive no heparin. During the trial period 40 patients defaulted from the trial (27 in the heparin and 13 in the no heparin group); 39 patients required "early" cardiac catheterization (23 in the no heparin and 16 in the heparin group). Figure 1 shows the patient flow from the time of randomization to follow-up.

Baseline characteristics and clinical follow-up. Tables 1 and 2, respectively, show the demographic data for the two groups after default and lesion characteristics before and after default. The baseline characteristics of both groups were well matched. Clinical follow-up data were available from all patients not defaulting from the trial. During the course of the

Table 1. Patient Characteristics of the No Heparin and Heparin Groups After Default of 40 Patients

	No Heparin Group (139 pts, 174 lesions)	Heparin Group (140 pts, 161 lesions)
Men (%)	82	80
Age (yr) (mean ± SD)	56.2 ± 7	56.7 ± 9
Smoker	48	56
Diabetes	11	7
Hypertension	31	26
Hyperlipidemia	29	26
Previous MI	71	64
Previous CABG	6	3
Previous PTCA	3	4
Drug therapy		
Aspirin	122	109
Calcium antagonists	106	101
Nitrates	104	91
Beta-blockers	102	96
Angina grade		
0	0	0
1	4	3
2	81	73
3	55	49
4	19	15
Duration of angina (mo)		
<6	40	41
6–12	53	42
12–24	21	18
>24	45	39

Unless otherwise indicated, data are expressed as number of patients. CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; pts = patients.

JACC Vol. 26, No. 4
October 1995:947–54

Table 2. Vessel and Lesion Characteristics of the Heparin and No Heparin Groups Before and After Default

	No Heparin Group		Heparin Group	
	Pre	Post	Pre	Post
Vessels	188	174	189	161
Vessel dilated				
LAD	100	95	100	87
RCA	46	42	49	40
LCx	42	37	40	34
Sites dilated (no.)				
1	160	150	150	124
2	12	16	15	14
3	0	0	3	3
4	1	1	0	0
Lesion characteristic				
A	64	59	67	57
B	97	91	104	92
C	27	24	18	12
Dissections (no.)	38	33	34	27
Dissection grade				
A	14	12	10	9
B	13	13	12	9
C	9	7	10	8
D	2	1	2	1
E	0	0	0	0
Reference artery/ balloon ratio	0.96/0.17	0.17/0.2	0.90/0.14	1.0/0.2

Unless otherwise indicated, data are expressed as number of vessels. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; Pre (Post) = before (after) default; RCA = right coronary artery.

Table 3. Minimal Lumen Diameters and Clinical Outcome of Patients Undergoing "Early" (<4 mo) Repeat Cardiac Catheterization

	No Heparin Group (n = 23)	Heparin Group (n = 16)
Reference diameter (mm)		
Pre PTCA	2.81 ± 0.56	2.71 ± 0.50
Post PTCA	2.86 ± 0.49	2.69 ± 0.55
Follow-up	2.76 ± 0.46	2.76 ± 0.55
Minimal lumen diameter (mm)		
Pre PTCA	0.68 ± 0.42	0.78 ± 0.31
Post PTCA	1.78 ± 0.42	1.76 ± 0.48
Follow-up	0.96 ± 0.71	1.18 ± 0.59
% diameter reduction		
Pre PTCA	75.3 ± 15	72.3 ± 10
Post PTCA	37.1 ± 14	34.5 ± 11
Follow-up	64.6 ± 25	57.3 ± 20
Angina grade (CCS class)		
Mean	2.6	2.6
Range	2–4	1–4
Repeat catheterization at (wk)		
Mean	8.5	7.5
Range	1–14	0.5–12
Repeat PTCA	12	6
CABG	5	5
Medical therapy	6	5

Unless otherwise indicated, data are presented as number of patients or mean value ± SD. CCS class = Canadian Cardiovascular Society classification; other abbreviations as in Tables 1 and 2.

study two patients (one patient in each group) died, both of myocardial infarction. Ten patients (5 in each group) underwent coronary bypass surgery and 18 (12 in the no heparin and 6 in the heparin group) had repeat coronary angioplasty. At the 4-month assessment, 33% of patients in the no heparin and 32% of those in the heparin group reported recurrent angina.

Angiographic analysis. During the study period, 39 patients underwent "early" cardiac catheterization because anginal symptoms had recurred (23 patients in the no heparin group and 16 in the heparin group). Table 3 shows the reference diameters, minimal lumen diameters, restenosis rates and clinical outcome of the patients undergoing early catheterization. The minimal lumen diameters before and after coronary angioplasty and at follow-up were not significantly different at any time between the two patient groups. As assessed by a definition of "loss of 50% of the absolute gain," 19 patients in the no heparin and 9 in the heparin group had restenosis, (chi-square test, p = 0.15, odds ratio 0.27, 95% confidence interval [CI] −0.06 to 1.2). There were no significant differences in restenosis rates or changes in minimal lumen diameter between patients with early or elective follow-up angiography.

Figure 2 shows the quantitative angiographic details of the two groups at elective follow-up. For those patients undergoing elective repeat coronary angiography, the difference between the minimal lumen diameter at follow-up and immediately after angioplasty was −0.49 ± 0.57 mm in the no heparin group and −0.41 ± 0.57 mm in the heparin group. The 0.88-mm difference—that is, the treatment effect—was not significant (p = 0.22, 95% CI −0.05 to 0.22). As assessed by a categoric definition of loss of 50% of the absolute gain, the restenosis rate was 46% in the no heparin and 39% in the heparin group (chi-square test, p = 0.32, odds ratio 0.75, 95% CI 0.46 to 1.2). For all patients (those with early and elective restudy), the loss at follow-up in minimal lumen diameter was −0.55 ± 0.58 mm for the no heparin and −0.43 ± 0.59 mm in the heparin group (Table 4). The overall treatment effect was 0.12 mm (p = 0.07, 95% CI −0.004 to −0.25 mm), which corresponded to a restenosis rate of 51% in the no heparin and 41% in the heparin group (p = 0.09).

Figures 3 and 4 represent a cumulative frequency curve of the minimal lumen diameter and a plot of relative loss versus relative gain for the two groups.

Treadmill exercise tests. At follow-up 85% of patients in the no heparin and 86% of those in the heparin group underwent a standard treadmill exercise test (Bruce protocol). There were no differences between groups in the number of patients reporting pain or having significant ST changes during the test.

Acceptability of heparin treatment. The number of patients randomized into the study represents 92% of the patients approached. The main reason for nonenrollment was unwillingness to self administer heparin. Indeed, the major

JACC Vol. 26, No. 4
October 1995:947–54

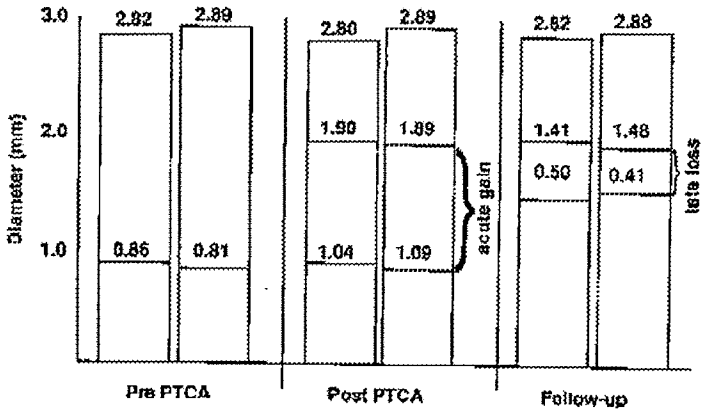


Figure 2. Reference diameters, minimal lumen diameters before (Pre) and immediately after (Post) percutaneous transluminal coronary angioplasty (PTCA) and at follow-up for the two groups. Acute gain and late loss are also shown.

reason for default was the inconvenient nature of the treatment. Three patients were withdrawn from the study as a result of pruritic swellings at the site of the injections that resolved on discontinuation of treatment. No cases of thrombocytopenia were reported and the occurrence of osteoporosis in one patient in each group is of doubtful significance. Apart from two instances of bleeding at the femoral puncture site, no patients reported spontaneous bruising or troublesome hematoma formation after minor trauma. The treatment, although onerous, would appear to be safe and generally well tolerated.

Table 4. Absolute Measurements of Reference Diameters and Obstruction Diameters for All Patients Undergoing Repeat Catheterization

	No Heparin Group (159 pts, 174 lesions)	Heparin Group (140 pts, 161 lesions)
Reference diameter (mm)		
Pre PTCA	2.82 ± 0.54	2.87 ± 0.54
Post PTCA	2.81 ± 0.50	2.87 ± 0.51
Follow-up	2.81 ± 0.50	2.87 ± 0.52
Minimal lumen diameter (mm)		
Pre PTCA	0.83 ± 0.37	0.81 ± 0.34
Post PTCA	1.91 ± 0.46	1.88 ± 0.48
Follow-up	1.36 ± 0.63	1.45 ± 0.64
Acute gain (mm)	1.08 ± 0.48	1.07 ± 0.49
Relative gain	0.39 ± 0.18	0.38 ± 0.15
Late loss (mm)	0.55 ± 0.58	0.43 ± 0.59
Relative loss	0.20 ± 0.22	0.15 ± 0.21
Net gain index	0.19 ± 0.22	0.22 ± 0.20
Percent stenosis		
Pre PTCA	71.5 ± 12%	71.9 ± 10%
Post PTCA	31.6 ± 13%	35.4 ± 12%
Follow-up	52.0 ± 21%	50.0 ± 19%
Restenosis rate (loss 50% absolute gain)		
Patients	51%	41%
Vessels	48%	39%

*Unless otherwise indicated, data are expressed as mean value ± SD. Abbreviations as in Tables 1 and 2.

Discussion

Although the effects of heparin on smooth muscle cell proliferation have been known for some time, the precise mode of action is unclear. Heparin binds to smooth muscle cells and is taken up by both receptor-mediated and slower endocytotic pathways (22). Studies utilizing ornithine decarboxylase activity and tritiated thymidine uptake suggest that heparin acts either at the late G1 or early S phase of the cell cycle, with consequent reduction in synthesis of deoxyribonucleic acid and ribonucleic acid (23). Heparin may also have secondary effects due to a reduction in expression of growth factor receptors (24), or enhanced action of growth inhibitory factors (25) such as transforming growth factor B.

There are few studies in humans addressing the effect of heparin on restenosis after coronary angioplasty. The trial by Ellis et al. (26), randomly assigned 416 patients to receive either intravenous heparin or dextrose for 18 to 24 h after coronary angioplasty. The restenosis rates were 41.2% in the heparin group and 36.7% in the control group when assessed at 6 months (restenosis defined as >50% diameter stenosis at follow-up). Similar results were obtained by Saenz et al. (27), although their study had considerably fewer patients. For similar reasons little meaningful data could be derived from the study by Lehmann et al. (28), which was terminated early on ethical grounds because 82% of the 23 patients at follow-up had restenosis. More data are available from the Enoxaparin study (17) involving 465 patients who were randomized to low molecular weight heparin (30 mg subcutaneously daily) or placebo for 1 month. As assessed from clinical end points, the restenosis rate was 51% in the treatment group and 49% in the control group. There was no significant difference in the change in minimal lumen diameter at follow-up (0.49 and 0.5 mm, respectively, for the control and the treatment groups).

There has been some debate as to whether the commercially available low molecular weight heparin contains all of the antiproliferative effects of the subfractions outlined in the publications by Guyton et al. (10) and Hoover et al. (29).

JACC Vol. 28, No. 4
October 1996:947–54

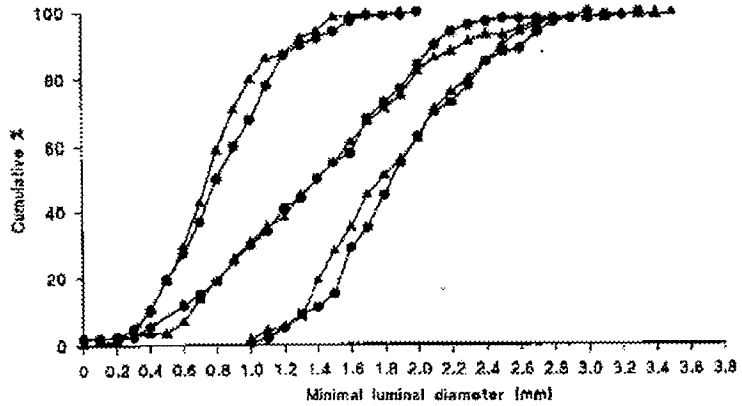
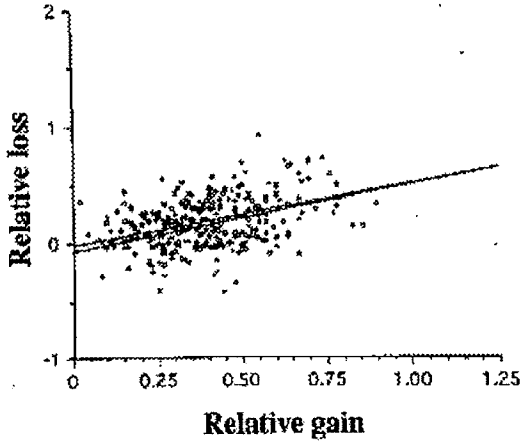


Figure 3. Cumulative frequency curves of minimal lumen diameters for the heparin (triangles) and no heparin (circles) groups before and immediately after coronary angioplasty and at follow-up.

Commercially available low molecular weight heparin may not be the same subfraction as that used in experimental models. For this reason we chose to examine the effects of unfractionated heparin, knowing also that any retained antithrombotic effects of the unfractionated heparin may also be beneficial if thrombus formation is another smooth muscle cell stimulus (30). We chose to give the heparin for a total of 4 months because data suggest that 90% of restenosis if it is to occur will occur within this time. Although the process of smooth muscle cell proliferation takes place in the first few days, we chose not to risk merely delaying the process by limiting the time of heparin administration to this period.

Despite the advantages of using this relatively high dose of unfractionated heparin given over the known course of the restenotic process, we have shown that this treatment failed to beneficially influence either the angiographic outcome (amount of intimal hyperplasia) or the clinical outcome. There may have been several reasons for these findings.

Figure 4. Plot of relative loss versus relative gain for the heparin (plus signs) and no heparin (circles) groups.



Study power. Currently the power of any trial is determined by the effect one wants to achieve (31). Thus a 10% reduction requires larger numbers than if a 50% reduction is the aim. The use by other investigators of a 33% reduction (resulting in trial numbers of 230 patients/group) is as arbitrary as any other present reduction. Our choice was based on in vitro studies. However, for the secondary end points (clinical outcome) the study power was too small.

Heparin dose. The dose of heparin selected for this trial was based on both ethical and pharmacologic considerations. At the time of the study's inception, the largest available dose of "ready to use" heparin was 12,500 IU. Our dose of 25,000 IU of heparin daily approaches doses that could result in a significant risk that patients would develop osteoporosis (32). Additionally, the statements of patients interviewed before the trial, but not part of it, indicated that asking patients to self-inject this drug more than twice daily would be unacceptable.

From our own laboratory work using cultured human smooth muscle cells we found that concentrations of heparin that could be achieved by subcutaneous injection of 12,500 IU (i.e., 0.3 IU/ml), significantly inhibited smooth muscle cell proliferation. Castellot et al. (33) have shown that 1 to 5 μg of heparin added to growth media could produce inhibition of smooth muscle cells in culture. However, in vivo work suggests that higher doses are required to produce a significant inhibition of smooth muscle cell proliferation. Clowes and Karnovsky (9), using the rat carotid model, reported that 50 to 100 IU/kg body weight per h was needed to produce significant inhibition of cell proliferation. Likewise, using hypercholesterolemic rabbits, Currier et al. (13) showed that 10 mg/kg per day of enoxaparin could reduce the restenosis rate in iliac arteries, but human studies (17) using 30 mg/day showed no benefit.

Thus, although we used the largest ethically acceptable dose, this dose may have been too small to locally inhibit smooth muscle cell proliferation. There has been a suggestion, perhaps a justification of negative results, that humans are

more sensitive than animals to many of the drugs tried systemically, and thus the dosage issue is not relevant. However, in the light of our results, it is reasonable to conclude that human vascular smooth muscle cells are no more sensitive than animal smooth muscle cells to the effects of heparin; otherwise, some beneficial effect ought to have been observed with this smaller dose.

Conclusions. The failure of unfractionated heparin to show any benefit in humans despite encouraging results in animal models is similar to the outcome of trials with cilazapril (34), enoxaparin (17) and ketanserin (35). The ability of heparin to inhibit vascular smooth muscle cell growth in vitro and in animal models of vascular injury is well documented. It appears not to have the therapeutic efficacy to reduce restenosis after angioplasty in humans. The published results of intravenous short-term administration (24 to 48 h) of heparin and the results of medium-term (1 month) of low molecular weight heparin also show no benefit. The reasons for these findings have been addressed by other trialists studying other drugs, namely the discrepancy between systemic doses that work in animals and those that can be given to humans. The argument that smooth muscle cells or the mechanisms stimulating them are more sensitive in humans appears not to hold. Although we undertook a study with heparin given in as large a dose that was believed to be safe and ethical, it is clear that attention will need to be turned to methods of local delivery that will permit administration of doses that affect the process without adversely affecting the patient. Perhaps before heparin is finally rejected as a "magic bullet" for the prevention of restenosis, clinical trials should be conducted that match animal studies with continuous infusions or by local targeted delivery.

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Appendix

Definitions of Lesion Characteristics and Dissection Grades (Table 2)

Lesion Characteristics

Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Type B: Contrast extravasation parallel to the lumen of the vessel disappearing with the passage of the contrast material.

Type C: Contrast extravasation persisting after passage of the contrast material.

Type D: Spiral-shaped filling defect with normal (D1) or delayed (D2) anterograde flow.

Type E: Persistent lumen filling defect with delayed runoff of the contrast material in the distal vessel.

Type F: Filling defect accompanied by total occlusion.

Dissection Characteristics

Type A: Discrete, concentric, readily accessible, smooth contour, nonangulated segment, no calcification, not occlusive, not ostial, no major branch involvement, absence of thrombus.

Type B: Tubular, eccentric, moderate tortuosity, moderately angulated segment, irregular contour, moderate calcification, total occlusion <3 months, ostial site, bifurcation lesion, thrombus present.

Type C: Diffuse, very tortuous, markedly angulated, total occlusion >3 months, inability to protect side branch.

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A RANDOMIZED COMPARISON OF CORONARY-STENT PLACEMENT AND BALLOON ANGIOPLASTY IN THE TREATMENT OF CORONARY ARTERY DISEASE

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Abstract *Background.* Coronary-stent placement is a new technique in which a balloon-expandable, stainless-steel, slotted tube is implanted at the site of a coronary stenosis. The purpose of this study was to compare the effects of stent placement and standard balloon angioplasty on angiographically detected restenosis and clinical outcomes.

Methods. We randomly assigned 410 patients with symptomatic coronary disease to elective placement of a Palmaz–Schatz stent or to standard balloon angioplasty. Coronary angiography was performed at base line, immediately after the procedure, and six months later.

Results. The patients who underwent stenting had a higher rate of procedural success than those who underwent standard balloon angioplasty (96.1 percent vs. 89.6 percent, P = 0.011), a larger immediate increase in the diameter of the lumen (1.72±0.46 vs. 1.23±0.48 mm, P<0.001), and a larger luminal diameter immediately after the procedure (2.49±0.43 vs. 1.99±0.47 mm, P<0.001). At six months, the patients with stented lesions continued to have a larger luminal diameter (1.74±0.60 vs. 1.56±0.65 mm, P = 0.007) and a lower rate of restenosis (31.6 percent vs. 42.1 percent, P = 0.046) than those treated with balloon angioplasty. There were no coronary events (death; myocardial infarction; coronary-artery bypass surgery; vessel closure, including stent thrombosis; or repeated angioplasty) in 80.5 percent of the patients in the stent group and 76.2 percent of those in the angioplasty group (P = 0.16). Revascularization of the original target lesion because of recurrent myocardial ischemia was performed less frequently in the stent group than in the angioplasty group (10.2 percent vs. 15.4 percent, P = 0.06).

Conclusions. In selected patients, placement of an intracoronary stent, as compared with balloon angioplasty, results in an improved rate of procedural success, a lower rate of angiographically detected restenosis, a similar rate of clinical events after six months, and a less frequent need for revascularization of the original coronary lesion. (N Engl J Med 1994;331:496-501.)

THE long-term benefit of coronary balloon angioplasty is limited by the possibility of restenosis of the treated segment, which occurs in approximately 30 to 50 percent of patients.[1-4] Restenosis can be caused by several factors, including elastic recoil of the dilated artery, platelet-mediated thrombus formation, proliferation of smooth-muscle cells, and vascular remodeling.[5] When restenosis develops, it is frequently associated with recurrent myocardial ischemia that necessitates additional revascularization procedures. New approaches to coronary intervention have therefore been developed with the aim of reducing the possibility of restenosis. Debulking coronary atheroma with lasers or atherectomy has not improved the problem of restenosis.[6-9] However, preliminary evidence suggests that stents may reduce the chance of restenosis by decreasing the elastic recoil of the vessel and sealing intimal flaps, thus providing a wider, smoother coronary lumen.[10,11] To test this hypothesis, we conducted a prospective, randomized trial to compare the rates of restenosis with coronary-stent placement and standard balloon angioplasty.

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*Additional participants in the Stent Restenosis Study (STRESS) trial are listed in the Appendix.

METHODS

Participating Centers and Investigators

The study centers and investigators were selected on the basis of their experience with implantation of Palmaz–Schatz coronary stents. The study protocol was approved by the institutional review board at each of the 20 centers participating in the trial.

Patient Selection

The study population consisted of patients with symptomatic ischemic heart disease and new lesions of the native coronary circulation. The specific angiographic criteria for enrollment included at least 70 percent stenosis, according to the estimate of the investigators; a lesion that was 15 mm or less in length and could be spanned by a single stent; and a vessel diameter of at least 3.0 mm. The criteria for exclusion were a myocardial infarction within the previous seven days; a contraindication to aspirin, dipyridamole, or warfarin sodium; and a left ventricular ejection fraction of 40 percent or less. The angiographic criteria for exclusion were evidence of coronary thrombus, the presence of multiple focal lesions or diffuse disease, serious disease in the left main coronary artery, ostial lesions, and severe vessel tortuosity.

Randomization

After the patients had been interviewed to determine their eligibility and had given their informed consent, they were randomly

assigned to either stent placement or balloon angioplasty. Randomization of the patients, stratified according to center with a block design, was carried out by means of sealed envelopes. The randomization sequence was developed so that an equal number of patients would be assigned to each treatment at each center.

Procedural Protocol

Stent Placement

The Palmaz–Schatz stent is composed of two rigid 7-mm slotted stainless-steel tubes connected by a 1-mm central bridging strut (Johnson and Johnson Interventional Systems, Warren, N.J.). The stent, which is 1.6 mm in diameter in the unexpanded state, is mounted on a balloon catheter and protected by an outer sheath during passage to the target site. When the sheath is withdrawn, inflation of the balloon catheter expands the stent. Technical details of the design and placement of the Palmaz–Schatz coronary stent have been described elsewhere.[12,13]

Patients assigned to stent placement received nonenteric aspirin (325 mg daily), dipyridamole (75 mg three times a day), and treatment with a calcium-channel antagonist, initiated at least 24 hours before the procedure. In addition, patients received intravenous low-molecular-weight dextran (dextran 40, given at a dose of 100 ml per hour for two hours before stenting and at a dose of 50 ml per hour during and after the procedure, for a total volume of 1 liter). During the procedure, patients received an initial bolus injection of heparin (10,000 to 15,000 units) supplemented as needed to maintain an activated clotting time of more than 300 seconds. The heparin infusion was discontinued at the termination of the procedure and reinstituted four to six hours after hemostasis of the site of vascular access had been achieved. Warfarin sodium was begun on the day of the procedure. Heparin and warfarin sodium were both administered for at least 72 hours or until a prothrombin time of 16 to 18 seconds had been achieved (international normalized ratio, 2.0 to 3.5). After patients were discharged from the hospital, dipyridamole and warfarin sodium were continued for one month, and aspirin was continued indefinitely.

Angioplasty Protocol

Angioplasty was performed with the use of conventional techniques. Aspirin was prescribed, but warfarin sodium was not administered. Investigators attempted to achieve an optimal result with balloon angioplasty, which was defined as residual stenosis of less than 30 percent of the luminal diameter, according to a visual estimate. A crossover to stent placement was permitted as a "bail-out" procedure in the case of abrupt or threatened closure, defined as a dissection of the artery with compromised antegrade blood flow (Thrombolysis in Myocardial Infarction [TIMI] grade, <3) or persistent stenosis of over 50 percent of the luminal diameter in association with evidence of myocardial ischemia (chest pain, electrocardiographic changes, or both).

Follow-up

Patients were required to have clinical follow-up studies after one, three, and six months. Coronary angiography was required at six months in all the patients except those who had died or undergone coronary-artery bypass surgery or repeated angioplasty for abrupt closure during the first 14 days after the initial revascularization. Angiography performed before four months was allowed on the basis of clinical indications. However, if restenosis was not found, a subsequent angiogram was obtained after four months.

Angiographic Analysis

Angiography was performed in two orthogonal views. Intracoronary nitroglycerin (200 mg) was injected before all angiographic assessments. Angiograms were analyzed at the Core Angiographic Laboratory at Jefferson Medical College. Quantitative analysis was performed with the use of a validated edge-detection algorithm.[14] Vessel edges were determined with the computerized algorithm, and luminal diameters were measured with the dye-filled catheter as a reference. The diameters of the normal segments proximal and distal to the treated area were averaged to determine the reference diameter. The minimal luminal diameter, reference diameter, and percentage of stenosis were calculated as the mean values from two orthogonal projections. The percentage of elastic recoil was defined as the largest inflated-balloon diameter minus the postprocedural minimal luminal diameter divided by the inflated-balloon diameter. In addition, coronary lesions were assessed for eccentricity, calcification, thrombus, plaque ulceration, tortuosity, and postprocedural dissection. Definitions used for this morphologic analysis and prior validation studies of the quantitative angiographic analysis have been described elsewhere.[11,13,15]

End Points

The primary end point of the trial was angiographic evidence of restenosis, defined as at least 50 percent stenosis on the follow-up angiogram. Secondary angiographic end points included angiographic evidence of procedural success and the absolute minimal luminal diameter after the procedure and at follow-up. Angiographic evidence of procedural success was defined as a reduction in stenosis to 50 percent or less by quantitative analysis.

Clinical evidence of procedural success was defined as angiographic evidence of success without a major complication (death, myocardial infarction, or coronary-artery bypass surgery) during the index hospitalization. The secondary clinical end point was a composite end point, defined as whichever of the following occurred first: death, myocardial infarction, coronary bypass surgery, or the need for repeated angioplasty within the first 6 months (±60 days) after the initial revascularization. Myocardial infarction was documented by the presence of new Q waves of at least 0.04 second's duration or a creatine kinase level or MB fraction at least twice the upper limit of normal. Clinical events were classified as early (occurring from day 0 to day 14) or late (occurring after 14 days). Revascularization of the target lesion was defined as angioplasty or bypass surgery performed because of restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischemia, or both. Other events included abrupt vessel closure (after the patient had left the catheterization laboratory) and hemorrhagic complications, defined as a cerebrovascular accident, bleeding requiring transfusion, or the need for vascular surgery.

Clinical and angiographic data were forwarded to the Data Coordinating Center at the University of Pittsburgh for statistical analyses. Adverse events were audited and reviewed by members of the Steering Committee. The primary analysis of angiographic and procedural outcomes was based on the intention-to-treat principle. We also performed a secondary analysis of the rate of restenosis according to the treatment received.

For the analysis of continuous data, two-tailed t-tests were used to assess differences between the two treatment groups. The results are expressed as means ±SD. Categorical data, which are presented as rates, were compared by chi-square test, except for the composite clinical end point and revascularization of the target lesion, which were analyzed by means of Kaplan–Meier survival curves, with differences between the two treatment groups compared by Wilcoxon test.[16] Multiple linear regression was used to assess the relation between the luminal diameter at follow-up and multiple clinical and angiographic variables, including age, sex, location of the lesion, vessel diameter, and postprocedural luminal diameter.

Results

Between January 1991 and February 1993, 410 patients were enrolled in the study; 207 patients were randomly assigned to stent placement, and 203 to angioplasty. After randomization, three patients (two in the stent group and one in the angioplasty group) were excluded because they did not meet all the enrollment criteria. Thus, the final study group comprised 407 patients. Their base-line clinical and angiographic characteristics are shown in Table 1. More

men were assigned to the stent group than to the angioplasty group, and the patients in the stent group had lesions that were slightly longer, with a higher incidence of eccentricity, but the two groups were well matched with respect to other clinical characteristics.

Procedural and Early Clinical Outcome

Stents were placed in 197 of the 205 patients (96.1 percent) randomly assigned to this therapy. One patient, in whom stent placement failed because of an inability to cross the lesion with a guide wire, was treated medically. Seven patients were switched to angioplasty: three because of an inability to place the stent and four because of lesion characteristics deemed unfavorable for stent placement at the time of the procedure. In the angioplasty group, six patients required emergency coronary-artery bypass surgery. In addition, 15 patients were switched to alternative therapies: 14 (6.9 percent) to emergency stent placement as a bailout procedure (1 of the 14 subsequent required emergency bypass surgery) and 1 to directional atherectomy.

Table 1. Base-Line Clinical and Angiographic Characteristics of Patients Assigned to Stent Placement or Angioplasty.*

Characteristic	Stent Group (N = 205)	Angioplasty Group (N = 202)
Male — % of patients	83	73†
Age — yr	60±10	60±10
Diabetes — % of patients	15	16
Hypertension — % of patients	43	45
Hyperlipidemia — % of patients	44	48
Current smoker — % of patients	21	24
History of myocardial infarction — % of patients	37	36
Recent myocardial infarction (within previous 6 wk) — % of patients	18	15
Unstable angina — % of patients	47	48
Pain at rest	33	39
Pain with electrocardiographic changes	23	26
Postinfarction angina	7	6
No. of diseased vessels — % of patients		
1	64	68
2	27	21
3	9	11
Ejection fraction — %	61±12	61±11
Target vessel — % of patients		
Left anterior descending	47	48
Left circumflex	16	13
Right coronary artery	37	39
Calcification — % of patients	17	15
Thrombus — % of patients		
Definite	2	1
Possible	15	9
Eccentricity — % of patients	66	54‡
Lesion angulation >45° — % of patients	13	18
Lesion length — mm	9.6±3.0	8.7±2.7§
Stenosis — % of luminal diameter	75±9	75±8

*Plus–minus values are means ±SD.
†P≤0.05.
‡P = 0.02.
§P<0.001.

Table 2. Procedural Outcomes and Clinical Events.

Variable	Stent Group (N = 205)	Angioplasty Group (N = 202)	P Value
	% of patients		
Procedural outcome			
Angiographic success			
Reading at study center	99.5	96.5	0.04
Quantitative analysis	99.5	92.6	<0.001
Clinical success	96.1	89.6	0.011
Early events (0–14 days)			
Death	0	1.5	0.12
Myocardial infarction/Q wave	5.4/2.9	5.0/3.0	0.85/1.0
Coronary bypass surgery	2.4	4.0	0.38
Abrupt closure*	3.4	1.5	0.34
Repeated angioplasty	2.0	1.0	0.69
Any event	5.9	7.9	0.41
Late events (15–240 days)			
Death	1.5	0	0.25
Myocardial infarction/Q wave	1.5/1.0	2.0/0.5	0.72/1.0
Coronary bypass surgery	2.4	4.5	0.26
Repeated angioplasty	9.8	11.4	0.59
Target-vessel revascularization	10.2	15.4	0.06
Any event	15.1	15.8	0.84
All events (0–240 days)			
Death	1.5	1.5	0.99
Myocardial infarction/Q wave	6.3/3.4	6.9/3.5	0.81/0.9
Coronary bypass surgery	4.9	8.4	0.15
Repeated angioplasty	11.2	12.4	0.72
Any event	19.5	23.8	0.16
Bleeding and vascular complications			
Cerebrovascular accident	1.0	0.5	1.0
Surgical vascular repair	3.9	2.0	0.25
Bleeding requiring transfusion	4.9	2.5	0.11
Any event	7.3	4.0	0.14

*After the patient left the catheterization laboratory.

Procedural and early clinical outcomes are shown in Table 2. According to the quantitative analysis there was angiographic evidence of procedural success in 204 of the 205 patients (99.5 percent) randomly assigned to undergo stent placement and in 187 of the 202 patients (92.6 percent) randomly assigned to undergo angioplasty (P<0.001). The clinical success rates were 96.1 percent and 89.6 percent, respectively (P = 0.011).

Abrupt vessel closure occurred in 10 patients after they had left the catheterization laboratory: 7 in the stent group and 3 in the angioplasty group (3.4 and 1.5 percent, respectively; P = 0.34). In the three patients in the angioplasty group, the closure occurred after the stent had been placed as a bailout measure. Abrupt closure occurred an average of 6 days (range 2 to 14) after the procedure, and in 6 of the 10 patients, it occurred after hospital discharge. All the patients with abrupt closures had major cardiac events (two died and eight had nonfatal myocardial infarctions). The proportions of patients with any major cardiac event (death, myocardial infarction, coronary bypass surgery, or repeated angioplasty within 14 days after the procedure) were 5.9 percent in the stent group and 7.9 percent in the angioplasty group

(Table 2). Bleeding and vascular complications occurred more commonly in the stent group than in the angioplasty group (7.3 percent vs. 4.0 percent, P = 0.14). The hospital stay after the procedure was longer in the stent group (5.8 days vs. 2.8 days, P<0.001).

Angiographic Results

Angiography was repeated at six months in 336 of the 383 patients (88 percent) eligible for follow-up. Angiography was not repeated in 28 patients in the stent group because of refusal (15 patients) or ineligibility due to stent thrombosis (7), death (3), early coronary bypass surgery (2), or inability to perform the study procedures (1). In the angioplasty group, 43 patients did not have follow-up angiography because of refusal (32) or ineligibility due to early coronary bypass surgery (7), abrupt vessel closure (3), or death (1). The rate of restenosis was 31.6 percent (56 of 177 patients) in the stent group and 42.1 percent (67 of 159) in the angioplasty group (P = 0.046). The rates of restenosis among the patients who received their assigned therapy were 30.0 percent in the stent group and 43.0 percent in the angioplasty group (P = 0.016).

The luminal dimensions at base line, immediately after the procedure, and at follow-up are shown in Table 3. At base line, there was no difference in the reference diameter or the severity of stenosis between the two groups. After the procedure, a larger immediate gain in the luminal diameter was achieved in the patients who underwent stent placement than in those who underwent angioplasty, resulting in a larger mean (±SD) diameter in the stent group (2.49±0.43 vs. 1.99±0.47 mm, P<0.001). At follow-up, the stent group had a larger mean reduction in the luminal diameter (0.74±0.58 vs. 0.38±0.66 mm, P<0.001) but a larger net gain, resulting in a larger luminal diameter at follow-up (1.74±0.60 vs. 1.56±0.65 mm, P = 0.007). These data are shown in Figure 1. A stepwise linear regression analysis showed that the luminal diameter immediately after the procedure was the most important predictor of the luminal diameter at six months (b = 0.41, P<0.001), irrespective of the procedure used. Additional important determinants included a larger reference diameter (b = 0.31, P<0.001) and location of the lesion in a vessel other than the left anterior descending coronary artery (b = 0.14, P = 0.029).

Late Clinical Follow-up

Data on late cardiac events and all events are shown in Table 2. Clinical follow-up data were available for 406 of the 407 patients. Although the numbers of patients who died or had myocardial infarctions were comparable in the two groups, fewer patients in the stent group underwent revascularization of the target lesion (10.2 percent vs. 15.4 percent, P = 0.06) (Fig. 2). Event-free survival was 80.5 percent in the stent group, as compared with 76.2 percent in the angioplasty group (P = 0.16) (Fig. 3). Among the patients eligible for follow-up, a larger proportion of those in the stent group remained free of angina (78.9 percent vs. 71.1 percent, P = 0.076).

Table 3. Angiographic Results in the Stent and Angioplasty Groups.*

Variable	Stent Group (N = 205)	Angioplasty Group (N = 202)	P Value
Before the procedure			
Reference vessel (mm)	3.03±0.42	2.99±0.50	0.30
Minimal luminal diameter (mm)	0.77±0.27	0.75±0.25	0.48
Stenosis (% of luminal diameter)	75±9	75±8	0.81
After the procedure			
Reference vessel (mm)	3.05±0.40	2.99±0.46	0.15
Minimal luminal diameter (mm)	2.49±0.43	1.99±0.47	<0.001
Stenosis (% of luminal diameter)	19±11	35±14	<0.001
Elastic recoil (%)	15±11	24±15	<0.001
Dissection (% of patients)	7	25	<0.001
At follow-up			
Reference vessel (mm)	3.00±0.41	2.98±0.49	0.74
Minimal luminal diameter (mm)	1.74±0.60	1.56±0.65	0.007
Stenosis (% of luminal diameter)	42±18	49±19	0.001
Restenosis (% of patients)	31.6	42.1	0.046
Change in minimal luminal diameter			
Immediate gain (mm)	1.72±0.46	1.23±0.48	<0.001
Late loss (mm)	0.74±0.58	0.38±0.66	<0.001
Net gain (mm)	0.98±0.62	0.80±0.63	0.01

*Plus–minus values are means ±SD. Immediate gain refers to the minimal luminal diameter immediately after the procedure minus the diameter before the procedure. Late loss refers to the minimal luminal diameter immediately after the procedure minus the diameter at follow-up. Net gain refers to the minimal luminal diameter at follow-up minus the diameter before the procedure.

Discussion

In this trial, we compared stent placement with balloon angioplasty for the treatment of new focal coronary stenoses in larger vessels; we found a reduc-

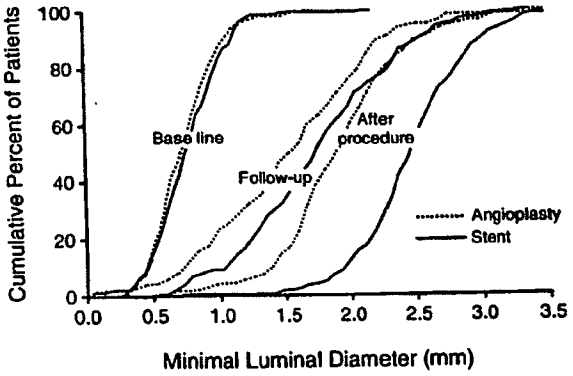

Figure 1. Minimal Diameter of the Lumen at Base Line, Immediately after Stent Placement or Angioplasty, and at Follow-up.

There was no difference in base-line values between the stent and angioplasty groups. Immediately after the procedure, the patients in the stent group had a larger minimal luminal diameter than those in the angioplasty group. Six months later, both groups had reduced values, and a significant difference in diameter persisted between the two groups.

tion in the rate of angiographic restenosis at six months with the stenting procedure. This reduction was associated with a reduction in the need for repeat revascularization due to ischemia-associated restenosis.

Our findings contrast with those of previous investigations that examined the efficacy of pharmacologic agents in preventing restenosis.[17-24] Of the newer interventional procedures, only directional atherectomy has been subjected to careful prospective, randomized studies to assess its efficacy in reducing restenosis, as compared with the efficacy of angioplasty.[7,8] Those studies showed either no benefit of atherectomy or a minimal reduction in restenosis with more frequent major complications.

Like the Coronary Angioplasty versus Excisional Atherectomy Trial (CAVEAT),[7] our study shows that the most important determinant of the luminal diameter at six months was the luminal diameter achieved immediately after the procedure. It seems plausible that the reduction in restenosis in our stent group was due to the significantly larger luminal diameter obtained immediately after placement of the stent, as compared with the luminal diameter immediately after angioplasty. The residual stenosis in the stent group (19 percent) was roughly half that in the angioplasty group (35 percent) and 10 percentage points less than the residual stenosis in patients undergoing directional atherectomy.[7] Although the larger immediate gain in luminal diameter was offset by a larger subsequent loss, the net gain remained larger in the patients in the stent group (Fig. 1). Multivariate analysis showed that the luminal diameter immediately after the procedure was the most powerful predictor of the luminal diameter at follow-up, regardless of whether stenting or balloon angioplasty achieved this result. Therefore, it was not the specific technique used, but rather its efficacy in achieving a larger luminal diameter that was the determining factor, an idea that has been suggested previously.[25] In addition, stenting resulted in a larger diameter with less risk of intimal disruption and elastic recoil, thereby acting as an effective intravascular scaffold. The ability of the stent to serve as a scaffold was further demonstrated in the 14 patients in the angioplasty group (6.9 percent) who were switched to stent placement for treatment of imminent or actual closure after balloon angioplasty had failed. At the inception of this trial, stent placement as a bailout measure, which at the time was not available as a routine procedure, was considered equivalent to emergency coronary-artery bypass surgery. Thirteen of the 14 patients who underwent stent placement as a bailout measure had balloon-induced dissections or luminal compromise associated with chest pain or electrocardiographic changes, suggesting that these patients would have had serious clinical events if stent placement had not been available. Therefore, the availability of stent placement probably decreased the rate of clinical events in the angioplasty group. This study thus represents a comparison of two treatment strategies: elective stent placement and elective balloon angioplasty with stent placement available as a bailout measure.

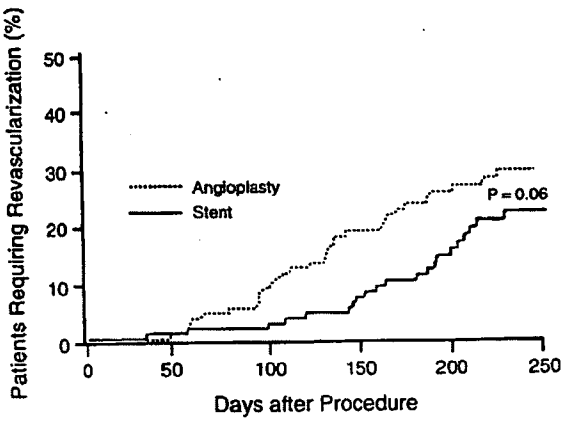

Figure 2. Kaplan–Meier Curves for Revascularization of the Target Lesion.

Fewer patients in the stent group than in the angioplasty group required revascularization of the target lesion because of ischemia.

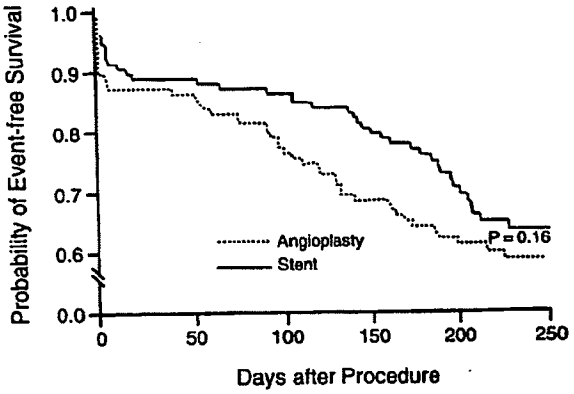

Figure 3. Kaplan–Meier Survival Curves for Major Cardiac Events (Death, Myocardial Infarction, Coronary-Artery Bypass Surgery, and Repeated Angioplasty).

Several limitations of stent placement need to be emphasized. Stent thrombosis occurred in 3.4 percent of the patients who underwent stent placement as an elective procedure and in 21.4 percent of those in whom stent placement was used as a bailout technique. These thrombotic events occurred 2 to 14 days after placement of the stent, with six instances of thrombosis after discharge, and invariably resulted in major clinical complications. Furthermore, the intense anticoagulation and antiplatelet regimen associated with stent placement resulted in nearly twice the number of hemorrhagic and peripheral vascular complications associated with angioplasty, as well as a prolonged hospital stay.

Although the frequency with which follow-up angiography was performed was relatively high in both

groups, there was a higher rate of angiographic follow-up in the stent group (92 percent vs. 83 percent, $P = 0.008$). This difference, which may bias the rate of restenosis in favor of stent placement, is a limitation of the study.

In conclusion, elective stent placement, as compared with angioplasty, has a higher clinical success rate and reduces the incidence of restenosis and the need for subsequent revascularization of the treated lesion. The reduction in restenosis is not associated with an increase in major cardiac events, despite the limitations imposed by stent thrombosis and hemorrhagic complications. The use of antithrombotic stent coatings, improved techniques to optimize expansion of the stent during implantation, and compression and closure devices at the site of arteriotomy may address these limitations. If they are effectively overcome, implantation of the Palmaz–Schatz stent may become the preferred treatment in selected patients with new lesions in large coronary arteries.

Appendix

The following institutions and investigators participated in the STRESS trial: Arizona Heart Institute, Phoenix (E. Davis, W. Catran, and K. Waters); Beth Israel Hospital, Boston (D.J. Diver, J. Carrozza, and C. Senerchia); Centro Cuore Columbus, Milan, Italy (Y. Almagor and M. Bernati); Cleveland Clinic Foundation, Cleveland (P. Whitlow); Florida Heart Hospital, Orlando (C. Curry, C.B. Saenz, W.H. Willis, Jr., R.J. Ivanhoe, and N. Granger); Hospital of the University of Pennsylvania, Philadelphia (H. Herman, D. Kolansky, W. Laskey, and D. DiAngelo); Johns Hopkins Hospital, Baltimore (V. Coombs); Lenox Hill Hospital, New York (E.M. Kreps, J. Strain, N. Cohen, J. Higgins, and C. Undemir); Scripps Clinic and Research Foundation, San Diego, Calif. (N. Morris and M. Dowling); St. Luke's Hospital, Houston (M. Harlan and B. Lambert); Thomas Jefferson University Hospital, Philadelphia (A. Zalewski, P. Walinsky, and D. Porter); Toronto General Hospital, Toronto (L. Lazzam, C. Lazzam, and P. Slaughter); University of Texas at San Antonio, San Antonio (J.P. Hennecken, S. Kiesz, and A. Briscoe); Vancouver General Hospital, Vancouver, B.C. (C.E. Buller and A. McCarthy); Victoria General Hospital, Halifax, N.S. (B. O'Neil, C.J. Foster, C.M. Peck, K.A. Foshay, and N.L. Fitzgerald); Victoria Hospital, London, Ont. (N. Murray-Parson and L. Marziali); Washington Cardiology Center, Washington, D.C. (K. Donovan); Yale University, New Haven, Conn. (H.S. Cabin and R.E. Rosen); *Data Coordinating Center:* Department of Epidemiology, University of Pittsburgh, Pittsburgh (K. Detre, V. Niedermeyer, L. Kennard, and L. Vetri); *Core Angiographic Laboratory:* Thomas Jefferson University Hospital, Philadelphia (R. Rake, S. Gebhardt, D.L. Fischman, M.P. Savage, and S. Goldberg); *Steering Committee:* D.S. Baim, S. Goldberg, M.B. Leon, I. Penn, and R.A. Schatz.

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5TH EDITION

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